Author response: Progressive neurodegeneration following spinal cord injury: Implications for clinical trials

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DOI: https://doi.org/10.1212/WNL.0000000000006540

Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: The state of clinical research in neurology

In their nationwide survey, Hall et al. reported that clinical research among American neurologists over the last decade has remained relatively stable. While rates of NIH funding remained steady during this period, Dr. Meador addresses an important concern that there has been a fall in grant applications among early career neurologists, who represent the future of academic neurology. In his commentary, Dr. Meador also acknowledges the significant reduction in the amount of time neurologists are permitted to dedicate to research and teaching over the last several decades. Institutional and industry-sponsored grants may augment the NIH research funding available for neurologists, but time remains a major roadblock for budding clinician-scientists.

James E. Siegler III, MD, and Steven Galetta, MD
Neurology® 2018;91:983. doi:10.1212/WNL.0000000000006536

Reader response: The state of clinical research in neurology

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Neurology® 2018;91:983. doi:10.1212/WNL.0000000000006539

Hall et al.[1] concluded that "The state of clinical research in neurology has remained relatively stable over the last 10 years." Sounds reassuring, but is it really? As noted, investigator-initiated research could not be distinguished from clinical trial participation.[1] Interactions with industry are critical to establishing new therapies and diagnostic devices, but important clinical research will never be addressed by industry. An increase in training opportunities for patient-oriented researchers was seen, but their effectiveness remains uncertain. Hall et al.[1] stated that "fewer neurology researchers are applying for NIH funding, with the greatest decrease found in the number of early career award applicants." The drop in early career applicants is particularly concerning for the future of academic neurology.

In a 2016 American Academy of Neurology survey, academic neurologists spent an average of 27.7% of their time on research and teaching combined (10% median time for each individually).[2] This represents a marked decrease from the mid 1980s, when the average combined time was 58%.[3] Thus, it is not surprising that the main barrier to conducting research listed by Hall et al.[1] was time (noted by 74% of clinical research responders). Thus, the state of clinical research in academic neurology remains a concern.[4,5]

1. Hall DA, Ramos AR, Gelfand JM, et al. The state of clinical research in neurology. Neurology 2018;90:e1347–e1354.
2. Busis NA, Shanafelt TD, Keran CM, et al. Burnout, career satisfaction, and well-being among US neurologists in 2016. Neurology 2017;88:797–808.
3. Schindler BA, Novack DH, Cohen DG, et al. The impact of the changing health care environment on the health and well-being of faculty at four medical schools. Acad Med 2006;81:27–34.
4. Meador KJ. Decline of clinical research in academic medical centers. Neurology 2015;85:1171–1176.
5. Meador KJ. Reader response: the state of academic neurology departments in the United States, 2016: a national survey. Neurology 2018;90:487–488.

Author disclosures are available upon request (journal@neurology.org).

Author response: The state of clinical research in neurology

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Neurology® 2018;91:984. doi:10.1212/WNL.0000000000006542

Dr. Meador makes excellent points regarding our article addressing the state of clinical research in neurology.[1] The results of the survey showed that some areas of clinical research had clearly worsened over the last 10 years, such as time spent on research or number of early career applicants to the NIH. These results are consistent with a recent report by Dr. Meador[2] addressing the decline of clinical research in academic medical centers. However, survey respondents reported improvement in other areas, including adequate support by institutional grants and the availability of training opportunities.[1] I agree that it will be important to monitor and address the drop in the pipeline of neurologists and neuroscientists focused on neuroscience research. I also agree that additional work is needed to distinguish changes within subgroups of researchers (such as between pharmaceutical-sponsored and investigator-initiated research), to clearly distinguish and to evaluate changes in funding mechanisms other than K or R awards over time, and to investigate individual pressures that decrease available time for research, such as the electronic medical record. Continued vigilance in these areas is critical to ensuring a robust network of clinical researchers in neuroscience that can bring the advances we need for our neurologic patients.

1. Hall DA, Ramos A, Gelfand JM, et al. The state of clinical research in neurology. Neurology 2018;90:e1347–e1354.
2. Meador KJ. Decline of clinical research in academic medical centers. Neurology 2015;85:1171–1176.

Editors' note: Progressive neurodegeneration following spinal cord injury: Implications for clinical trials

In an effort to determine radiographic predictors of clinical outcome following traumatic spinal cord injury (SCI), Ziegler et al. compared early and late brain/spine MRI findings between patients with SCI and healthy controls. While early signs of atrophy throughout white matter tracts herald poorer functional recovery in patients with acute SCI in this case-control study, Dr. Domingue reflects on the recovery—and eventual regression—he has seen among patients with spondylotic myelopathy. As the investigators from the case-control study acknowledge, the pathophysiology that underlies traumatic and nontraumatic SCI may result in variable patterns of disease progression. The authors emphasize that their observations on the MRI changes following spinal cord injury may provide outcome measures to study in clinical trials.

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Neurology® 2018;91:984. doi:10.1212/WNL.0000000000006538

Reader response: Progressive neurodegeneration following spinal cord injury: Implications for clinical trials

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Neurology® 2018;91:984–985. doi:10.1212/WNL.0000000000006541

In 37 years of general neurology practice, I have seen about 10 patients who had undergone cervical decompression for spondolytic myelopathy. Neurologic deficits (pain, weakness, spasticity) began

Author disclosures are available upon request (journal@neurology.org).

to progress after a period of stability; in some, improvement lasted years. At times, this deterioration was 5 or more years postdecompression. The imaging and other studies provided no explanations. The article by Ziegler et al.[1] on progressive neurodegeneration following spinal cord injury is the first I have found that may relate to this observation. Would the authors comment on the possible relationship of their findings to my observations?

1. Ziegler G, Grabher P, Thompson A, et al. Progressive neurodegeneration following spinal cord injury: implications for clinical trials. Neurology 2018;90:e1257–e1266.

Author response: Progressive neurodegeneration following spinal cord injury: Implications for clinical trials

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Neurology® 2018;91:985. doi:10.1212/WNL.0000000000006540

We agree with Dr. Domingue's observation that the trajectory of recovery after spinal cord injury (SCI) is complex and difficult to predict. We should clarify that in the present study, we investigated the effects of traumatic SCI on neurodegeneration across the neuroaxis.[1] However, we and others have shown that in cervical spondolytic myelopathy (i.e., nontraumatic SCI) remote tissue specific cord pathology is also evident.[2,3] Surprisingly, the extent of neurodegeneration is similar to traumatic SCI, although these patients with nontraumatic SCI had only mild clinical symptoms.[2] This suggests that, in a slow progressive disease (e.g., cervical spondolytic myelopathy), the CNS can compensate for neurodegenerative processes for much longer; however, with time, the competition between processes of reorganization and neurodegeneration is lost in favor of the latter. Nevertheless, the clinical viability of MRI-based structural measures for monitoring and predicting recovery after nontraumatic and traumatic SCI is feasible and will provide a tool to improve our understanding of the disease mechanism, which affects not only the spinal cord but also the brain after SCI.[3–5] These new insights will enable us to better predict individual recovery trajectories and identify patients who could profit from further interventions to delay, or even prevent, further clinical deterioration.

1. Ziegler G, Grabher P, Thompson A, et al. Progressive neurodegeneration following spinal cord injury: implications for clinical trials. Neurology 2018;90:e1257–e1266.
2. Grabher P, Mohammadi S, Trachsler A, et al. Voxel-based analysis of grey and white matter degeneration in cervical spondylotic myelopathy. Sci Rep 2016;6:24636.
3. Martin AR, De Leener B, Cohen-Adad J, et al. Monitoring for myelopathic progression with multiparametric quantitative MRI. PLoS One 2018;13:e0195733.
4. Freund P, Weiskopf N, Ashburner J, et al. MRI investigation of the sensorimotor cortex and the corticospinal tract after acute spinal cord injury: a prospective longitudinal study. Lancet Neurol 2013;12:873–881.
5. Freund P, Friston K, Thompson AJ, et al. Embodied neurology: an integrative framework for neurological disorders. Brain 2016;139:1855–1861.

Author disclosures are available upon request (journal@neurology.org).

Author response: Progressive neurodegeneration following spinal cord injury: Implications for clinical trials

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Neurology 2018;91;985
DOI 10.1212/WNL.0000000000006540